REMARKS

Discussion of Claim Amendments

Claims 16, 22, 25, 26, and 29 have been amended to include a reference to a "probe set". The term "probe set" is supported by the disclosure; see, for example, page 44, lines 13-15, disclosing a set of probes. Further, claims 16, 22, and 26 have been amended to recite "fluorescent dyes" and "base sequences" to appropriately reflect the use of the term "probe set". Claim 22 has been amended to delete the term "selected from the group consisting of the 287-316 site and the 342-371 site". Claim 22 also has been amended to recite that "the labeled oligonucleotide probe or probe set hybridizes to the specific mRNA expressed in the live cells". Claim 22 also has been amended to replace the term "fourth" with --third--, thereby correcting an obvious editing error in the third step. The term "capable of labeling the mRNA" in claim 22, first step, has been deleted as unnecessary.

New claims 30-33 have been added and are directed to embodiments of the invention. The reference to the probe or probe set capable of hybridizing to the 287-316 site and the 342-371 site in these claims is supported by the specification. Under the law, it is not necessary that the specification describe the claimed invention in *ipsis verbis* to satisfy the written description requirement. See, e.g., *In re Lukach*, 442 F.2d 967, 969, 169 USPQ 795, 796 (CCPA 1971). It is sufficient that the specification convey clearly to those skilled in the art the information that the applicant has invented the specific subject matter later claimed. See, e.g., *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976).

Applicants respectfully submit that the specification as originally filed satisfies the written description requirement for the new claims. For example, SEQ ID NO: 7-10 are described in Table 1 with an explanation of possible hybridization sites on IL-2 mRNA and the exact relation between SEQ ID NO: 7-10 and the human IL-2 mRNA sequence is described in Figure 1. SEQ ID NO: 7 is complementary to the 287-301 site on IL-2 mRNA and represents the sequence of a probe that hybridizes to nucleic acid 287-301 of the mRNA, and SEQ ID NO: 8 is complementary to the 302-316 site on IL-2 mRNA and represents the sequence of a probe that hybridizes to nucleic acid 302-316 of the mRNA. Furthermore, SEQ ID NO: 9 is complementary to the 342-356 site on IL-2 mRNA and represents the sequence of a probe that hybridizes to nucleic acid 342-356 of the mRNA, and SEQ ID NO:

10 is complementary to the 357-371 site on IL-2 mRNA and represents the sequence of a probe that hybridizes to nucleic acid 357-371 of the mRNA. Figure 6 and Figure 24 show that a probe set of IL-2 287-301(D) and IL-2 302-316(A), which is a probe set having the sequence of SEQ ID NO: 7 and SEQ ID NO: 8, respectively, as described in Table 3, hybridizes to IL-2 mRNA with high efficiency. Also, Figure 7 and Figure 24 show that a probe set of IL-2 342-356(D) and IL-2 357-371(A), which is a probe set having the sequence of SEQ ID NO: 9 and SEQ ID NO: 10, respectively, as described in Table 3, hybridizes to IL-2 mRNA with high efficiency. From these experimental results, those skilled in the art would readily appreciate that the 287-316 site and the 342-371 site have high accessibility for oligonucleotide hybridization, therefore the method of invention can be performed using an oligonucleotide probe or probe set capable of hybridizing to the 287-316 site or the 342-371 site of IL-2 mRNA, which is easily designed in reference to the sequence of the 287-316 site and the 342-371 site shown in Figure 1. Those skilled in the art would readily appreciate that applicants had possession of the invention of hybridizing to the 387-316 site as well the 342-371 site of the mRNA, and the nature of the disclosure, e.g. page 43, line 13 to page 45, line 12 and Figures 6, 7, and 24, is such that the disclosure clearly supports the claim limitations. For example, SEQ ID NO: 15-18 are described in Table 2 with an explanation of possible hybridization sites on IL-4 mRNA, and the exact relation between SEQ ID NO: 15-18 and the human IL-4 mRNA sequence is described in Figure 2. SEQ ID NO: 15 is complementary to the 176-190 site on IL-4 mRNA and represents the sequence of a probe that hybridizes to nucleic acid 176-190 of the mRNA and SEQ ID NO: 16 is complementary to the 191-205 site on IL-4 mRNA and represents the sequence of a probe that hybridizes to nucleic acid 191-205 of the mRNA. Furthermore, SEQ ID NO: 17 is complementary to the 265-279 site on IL-4 mRNA and represents the sequence of a probe that hybridizes to nucleic acid 265-279 of the mRNA and SEQ ID NO: 18 is complementary to the 280-294 site on IL-4 mRNA and represents the sequence of a probe that hybridizes to nucleic acid 280-294 of the mRNA. Figure 10 shows that a probe set of IL-4 176-190(D) and IL-4 191-205(A), which is a probe set having the sequence of SEQ ID NO: 15 and SEQ ID NO: 16, respectively, as described in Table 4, hybridizes to IL-4 mRNA with high efficiency. Also, Figure 11 shows that a probe set of IL-4 265-279(D) and IL-4 280-294(A), which is a probe set having the sequence of SEQ ID NO:17 and SEQ ID NO: 18, respectively, as described in Table 4, hybridizes to IL-4 mRNA with high efficiency. From these experimental results, those skilled in the art would

readily appreciate that the 176-205 site and the 265-294 site have high accessibility for oligonucleotide hybridization, therefore the method of invention can be performed using an oligonucleotide probe or probe set capable of hybridizing to the 176-205 site or the 265-294 site of IL-4 mRNA, which is easily designed in reference to the sequence of the 176-205 site and the 265-294 site shown in Figure 2. Those skilled in the art would readily appreciate that applicants had possession of the invention of hybridizing to the 176-205 site as well the 265-294 site of the mRNA.

No new matter has been added.

The Office Action

The Office Action sets forth the following grounds for rejection:

1. Claims 23-24 and 27-28 are objected to for an alleged informality;

2. Claims 22-29 are rejected under 35 USC § 112, 1ST paragraph, as allegedly containing new matter;

3. Claims 16-18 are rejected under 35 USC § 103(a), as allegedly unpatentable over Singer et al. (USP 5,728,527) in view of Graham et al. (USP 6,127,120);

4. Claims 19-21 are rejected under 35 USC § 103(a), as allegedly unpatentable over Singer et al. in view of Graham et al. and further in view of Levinson (USP 6,562,343); and

5. Claims 22-29 under the doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-2 of USP 6,872,525.

Reconsideration is respectfully requested.

Examiner Interview

Applicants wish to thank Examiner Ethan Whisenant for the courtesies extended to Xavier Pillai, one of applicants' attorneys, during the telephone interview held on October 26, 2005. The Examiner indicated that the drawings have been accepted by the Office. The Examiner also indicated that he will check the parent file for certified copies of priority documents. The Examiner also indicated that he will enter comments regarding the

acceptance of the drawings and the submission of priority documents in a future communication from the Office.

Discussion of Rejections

1. Informality Objection

Claims 23-24 and 27-28 are objected to for an alleged informality. This objection has been rendered moot as these claims have been canceled.

2. New Matter Rejection

Claims 22-29 are rejected under 35 USC § 112, first paragraph, for an alleged new matter. The Office Action states that there is no basis in the specification as originally filed for the limitation in claim 22 which reads "287-316 site and the 342-371 site" and the limitation in claim 26 which reads "176-205 site and the 265-294 site". The Office Action also states that there is no basis for the oligonucleotide sequences recited in claims 23-24 and 27-28. Applicants have canceled claims 23-24 and 27-28. Although Applicants disagree with the rejection, Applicants have deleted the limitations objected to in claims 22 and 26. New claims 30-33, which includes similar limitations are supported by the specification as discussed above. Accordingly, the present claims should not be rejected on this ground.

3. Obviousness Rejections

Claims 16-18 are rejected under 35 USC § 103(a), as allegedly unpatentable over Singer et al. in view of Graham et al. Claims 19-21 are rejected under 35 USC § 103(a), as allegedly unpatentable over Singer et al. in view of Graham et al. and further in view of Levinson. Applicants respectfully traverse the rejections.

The Office Action alleges that Singer et al. teaches a method of selectively separating live cells which have expressed a specific mRNA from a live cell group comprising all of the limitations recited in claims 16-17. The Office Action admits that Singer et al. fails to teach determining a site within the specific mRNA that has high accessibility for oligonucleotide probe hybridization and preparing an oligonucleotide probe, labeled with a fluorescent dye, having a base sequence capable of hybridizing to the base sequence of the thus determined site. However, the Office Action alleges that Graham et al. teaches that it was well known prior to the

instant invention that "mRNA has considerable secondary structure which can be predicted by computer modeling although this method is not satisfactory" and that "only certain regions of the mRNA are liable to be both single stranded and accessible for binding to an antisense oligonucleotides". The Office Action contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Singer et al. by the teachings of Graham et al. to arrive at the claimed invention. The Office Action further contends that claims 19-21 are obvious in view of the disclosures of Singer et al. and Graham et al. and further in view of Levinson, which allegedly teaches the identification separation and isolation of TH1 or TH2 cells based on the differential expression of certain proteins including cytokines.

To establish a *prima facie* case for obviousness, the Office must satisfy *three* requirements: (1) the prior art relied upon must contain some suggestion or incentive, coupled with knowledge generally available in the art at the time of the invention, that would have motivated those of ordinary skill in the art to modify a reference or combine the references. See, *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385, 58 USPQ2d 1286, 1293 (Fed. Cir. 2001) ("in holding an invention obvious in view of a combination of references, there must be some suggestion, motivation, or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in a way that would produce the claimed invention."); (2) the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, hindsight analysis is not allowed. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) ("While the idea of using a monkey gene to probe for a homologous human gene may have been obvious to try, many pitfalls existed that would have eliminated a reasonable expectation of successfully obtaining the EPO gene. Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious."); *and* (3) the prior art reference or combination of references must teach or suggest all the limitations of the claims. See *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art.").

Applicants respectfully submit that the Office failed to make a *prima facie* case for obviousness. Singer et al. requires a step of washing the cells to allow unhybridized probe to exit from the cell or tissue; see, e.g., "washing the cell or tissue to allow the excess unhybridized probe to exit the cell(s), and detecting specific hybridization of the probe", column 5, line 29, "excess probe had exited from the cells after about 1 to 2 hours incubation in medium", column 5, line 66, and "it has also been demonstrated that most of the probe was able to exit the cells during the wash step, apparently also by passive diffusion (Fig. 31 Example 7)", column 6, line 8, and also recited in claim 20 b) as one of the constituent features. Consequently, in Singer et al., specific hybridization is detected as a result of washing away unhybridized probe from cells, only when excess probe is able to exit from the cells.

On the contrary, the presently claimed invention does not require a washing step. The fluorescence can be advantageously measured without washing the cells to remove unhybridized probe molecules, as indicated by the claim 16 term "a third step of irradiating light to live cell group containing the live cells having hybridized and unhybridized oligonucleotide probe or probe set and the live cells having only unhybridized oligonucleotide probe or probe set and measuring the fluorescence which is emitted by the live cells".

Thus, an element of the claim is missing in the cited reference. When all elements of the claim are not found in the cited art, an obviousness rejection cannot stand. Singer et al., either alone or in combination with Graham et al. and Levinson, fails to suggest to those of ordinary skill in the art the presently claimed invention. Moreover, the present invention provides a clear advantage over Singer et al. by not requiring a washing step. In view of the foregoing, the obviousness rejection should be withdrawn. Claims 30-37 also should not be rejected on this basis.

4. Double Patenting Rejection

Claims 22-29 are rejected under the doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-2 of USP 6,872,525. Claims 23-24 and 27-28 have been canceled. New claims 30-33 have been added. As an administrative convenience, applicants enclose a Terminal Disclaimer. *Quad Environmental Technologies Corp. Union*

Sanitary Dist., 946 F.2d 870 (Fed. Cir. 1991). In view of the foregoing, the obviousness-type double patenting rejection should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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